Sarcoidosis: still a mystery?

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Sarcoidosis is a systemic granulomatous disease of unknown etiology. It has diverse clinical manifestations, most frequently including pulmonary disorders. It is associated with immunological abnormalities, the intricacies of which have yet to be clearly delineated. In the immunologically susceptible individual, genetic, environmental, nutritional, and socioeconomic factors may play a governing role in its development. Sarcoidosis is a diagnosis of exclusion established by clinical manifestations, radiologic findings, and histologic evidence of noncaseating epithelioid-cell granulomas in >1 organ. We will discuss parameters that are helpful in making this diagnosis.

The diagnostic criteria for sarcoidosis, initially proposed in the 1950s by the International Sarcoidosis Association, demanded that granulomas be present in ≥2 organs in the absence of a disease process that evokes a granulomatous response. A revised descriptive definition introduced by the International Conference on Sarcoidosis in 1975 states that sarcoidosis is a multisystem granulomatous disorder of unknown etiology, most often affecting young adults, in which patients present with hilar lymphadenopathy, pulmonary infiltration, and skin or eye lesions. This definition has remained despite advances in the understanding of the disease. In the first described case of sarcoidosis 120 years ago, it was called "livid papillary psoriasis" by Jonathan Hutchinson. The patient presented with purplish skin lesions and gout and later died of renal failure (1). Hutchinson suspected that this was a variant of mumps.

EPIDEMIOLOGY

Sarcoid has a worldwide distribution. It typically occurs in individuals between 20 and 40 years of age, and women are affected twice as often as men. African Americans are affected more than whites, at a ratio of 8:1, and the prevalence is 40 cases per 100,000 in the US population. The disease is more severe, chronic, and disabling in African Americans. White patients are more likely to present with acute symptoms yet often sustain remission with treatment. No veterinary equivalent for this disease has been found (2). This makes study of the disease process more difficult and, no doubt, has slowed progress.

ETIOLOGY

The cause of sarcoidosis remains unknown. Extensive research targeting infectious agents, chemicals, drugs, allergies, autoimmunities, and genetic factors has revealed no identifiable etiologic agent to account for the characteristic granuloma of sarcoidosis. In a study on a limited number of patients with systemic sarcoidosis, acid-fast coccobacillary forms were detected in biopsy materials. It was postulated that a form of cell wall–deficient bacteria, possibly related to mycobacteria or corynebacteria, may be a causative agent in some cases (2). The finding of mycobacterial DNA in the sarcoid lesions of a small group of patients suggests that mycobacteria or some of its components might be capable of inducing the B-cell immune response and pathologic changes of sarcoidosis (3). The T- and B-lymphocyte disturbances in sarcoid patients may also be attributed to the effects of a viral infection depressing T-cell function.

Hypersensitivity to inhalation of pine pollen, peanut dust, clay soil, or talc has also been incriminated as a causative factor in different geographic areas. The role of these environmental and organic antigens in the pathogenesis of sarcoidosis remains unclear, and no firm relationship has been demonstrated (2).

Various features of sarcoidosis may be associated with specific antigens of major histocompatibility loci. The occurrence of sarcoidosis in members of the same family has suggested the involvement of some genetic factor (4). The most interesting human leukocyte antigen association in sarcoidosis has been the presence of the B8 and DR3 types in patients with acute sarcoidosis. It was suggested that the B8, DR3 phenotype identifies a group of patients who are likely to develop acute sarcoid arthritis and hilar adenopathy that progresses to chronic disease (5).

PATHOLOGY

Sarcoidosis is characterized by the formation of discrete, noncaseating epithelioid-cell granulomas in all or at least 2 affected organs or tissues. Granulomata consist of focal collections of macrophages, a few multinucleated giant cells, and scanty surrounding lymphocytes. Langhans' giant cells and foreign body–type giant cells are identified around Schaumann's bodies. Fibrinoid necrosis is spotty and relatively inconspicuous; it may be present at the centers of the granulomata, proceeding to either complete resolution or conversion into hyalinized fibrous tissue (2). If necrosis is present in the granulomata, it is neces-

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sary to exclude an infective condition such as tuberculosis or deep-seated fungal infection.

Lymphohematogenous spread may occur, and the tissues most often affected are the lymph nodes (78% of patients), lung (77%), liver (67%), spleen (50%), heart (20%), and skin (16%). The eyes, lacrimal glands, and other tissues may become involved (2).

In the lung, the manifestations of sarcoid are most severe and may be the most disabling. Chronic sarcoidosis may lead to pulmonary fibrosis, which is most marked in the upper lobes. Bronchiectasis and emphysema may occur. Pleural involvement is common but causes few clinical symptoms, although pleural effusion may occur. Pulmonary vessel involvement with granuloma may occur, with a rare report of pulmonary hypertension if a vessel is occluded (6). Heart involvement with sarcoidosis may cause sudden death due to arrhythmia.

PATHOGENESIS

Evidence now supports the idea that sarcoidosis is primarily an immunologic disorder. The early stage of pulmonary sarcoidosis, as seen in tissue biopsy, exhibits a mononuclear cell infiltrate consisting of macrophages and T lymphocytes (2). Newly active granulomas are surrounded by large activated lymphocytes, mainly of the helper T-cell type that express $CD4^+$ surface antigens. As the granuloma becomes less active, there is a shift to predominance of suppressor $CD8^+$ T cells (7). This switch from $CD4^+$ to $CD8^+$ T cells may modulate granuloma maturation and progression (8).

In the pulmonary interstitium, granuloma maturation is accompanied by increasing numbers of lymphocytes in the bronchoalveolar lavage (BAL) fluid. Results from noninvasive induced sputum (IS) expectoration correlated with those of the BAL fluid. The $CD4^+$ to $CD8^+$ switch in IS and BAL fluid paralleled changes in disease status (i.e., progression) and staging, suggesting that IS may be used as a noninvasive surrogate to follow disease activity and response to treatment in patients with pulmonary sarcoid.

The $CD4^+$:$CD8^+$ ratio and tumor necrosis factor-alpha levels in IS and BAL did not correlate with other conventional parameters of disease activity, such as angiotensin-converting enzyme (ACE) levels and forced expiratory volume in 1 second (FEV_1) values. This is probably because each parameter measures different aspects of the disease process (8). D'Ippolito et al compared the cellular profiles of IS, BAL, and bronchial washings (BW) in patients newly diagnosed with sarcoidosis. The study demonstrated that IS of sarcoid patients had greater cellularity than IS of healthy controls and greater concentrations of lymphocytes than BW or BAL. There was also evidence of increased numbers of epithelial cells, suggesting that the inflammatory process involves the airway epithelium (9).

Interleukin (IL)-2 is involved in the pathogenesis of sarcoidosis via stimulation of T-cell proliferation at the sites of inflammation, differentiation of T lymphocytes into effector cells that produce lymphokines, and recruitment of additional helper T cells from peripheral blood (2). T lymphocytes induce the migration of monocytes to the site of disease by secreting chemotactic factors, the initial step in granuloma formation. Other lymphokines cause the activation and differentiation of recruited monocytes into activated macrophages, giant cells, and epithelioid cells, the characteristic cells of sarcoid granulomata (2).

The sarcoid antigen (S antigen) is recognized through the T-cell antigen receptor (TCR) expressed on the surface of T lymphocytes. In sarcoid BAL, the majority of T lymphocytes exhibit increased levels of mRNA transcripts for the beta chain of TCR. Alveolar macrophages might also serve as antigen-presenting cells and initiate the alveolitis seen in pulmonary sarcoidosis by presenting the mystery antigen to local and recruited lymphocytes (10). Increased IL-2 expression on sarcoid alveolar macrophages could be involved in macrophage activation. Sarcoid inflammation in the lung induces the emergence of a specific alveolar macrophage subset whose suppression of T-cell proliferation is enhanced in sarcoidosis. This subset of macrophages could arise as a part of a secondary response to stimuli in the immediate surroundings to contain reactions arising from the initial macrophage–T-cell interaction. This intricate macrophage-mediated regulation of local T-cell responses suggests that a sarcoid reaction would be self-limiting (11). Because even untreated patients can have spontaneous resolution of alveolitis, Bingisser et al hypothesized that down-modulating mechanisms such as anti-inflammatory cytokine IL-10 and transforming growth factor-beta were involved. They followed 32 patients with active sarcoid and found them to have significantly higher levels of alveolar macrophages, with spontaneous IL-10 production and secretion, but the same transforming growth factor-beta levels as controls (12).

HEMATOLOGIC FEATURES

Whereas in the lung the T cells appear activated and increased in number, the opposite is true in peripheral blood, where the T cell numbers are decreased. The response of the peripheral lymphocytes to antigen is impaired, and type IV hypersensitivity responses are depressed (2). Many patients with active sarcoid have partial to complete anergy to cutaneous antigens such as tuberculin, mumps virus, *Candida*, and others. Historically, this anergy was demonstrated by the Kveim reaction, in which a lymph node or other organ from a patient with active sarcoid was prepared for subcutaneous injection into the patient. The Kveim reaction differs from the classic delayed type IV hypersensitivity skin reaction. The delayed-type hypersensitivity reaction begins 8 hours after exposure, peaks at 24 to 48 hours, and resolves after 96 to 120 hours. The Kveim reaction takes 4 to 6 weeks to develop. This method of testing has been abandoned and is of historic interest only.

HUMORAL ASPECTS

Hyperreactivity of the humoral immune system has been observed in sarcoidosis. These humoral abnormalities include polyclonal elevation of gamma globulins in BAL of 70% of patients with active sarcoidosis (13). This abnormality is often associated with an exaggerated humoral response to certain common antigens, such as mycoplasma and respiratory viruses. The elevated level of immunoglobulin found in BAL and serum of sarcoid patients could reflect a defect in T-cell regulation of B-cell function, with consequent immunoglobulin synthesis by B cells at sites of inflammation and subsequent diffusion into the blood (14).

CLINICAL MANIFESTATION

Approximately 20% to 40% of patients with sarcoidosis are asymptomatic, and their disease is discovered by routine chest x-ray. Twenty-five percent present with cough and dyspnea, while an additional 25% present with eye, skin, or nasal complaints. Constitutional symptoms, such as fever, fatigue, malaise, or anorexia, are nonspecific and can be mild or severe. In most patients, manifestations disappear within a few months or years. In 10% to 15% of patients, however, the disease progresses to involve different organs and tissues with ensuing major chronic disability (15). The lung is involved most often and is probably one of the first sites to be affected (15). At least 90% of patients with sarcoidosis exhibit abnormalities on chest radiographs during the course of their disease, and the diagnosis is often found incidentally. Twenty percent to 25% develop a permanent loss of lung function in the form of a decrease in diffusion capacity without loss in lung volume, and 5% to 10% die from complications. The outlook is better when a patient presents with erythema nodosum and acute onset. An insidious onset may be followed by unrelenting progressive fibrosis (2).

DIAGNOSTIC AIDS

Guidelines on the management of sarcoidosis note that worsening respiratory symptoms, deterioration of lung function as seen on chest radiographs (vanishing lung), and bronchiectasis with cavity formation all signify progressive disease (2).

Radiologic staging for pulmonary sarcoidosis is valuable for assessing treatment response and following disease progression. The stages are as follows:

- Stage 0: normal chest radiograph (5% to 10% of patients with active disease)
- Stage 1: lymphadenopathy only (>50% of patients with active disease)
- Stage 2: lymphadenopathy associated with pulmonary infiltrates (25% to 30% of patients with active disease)
- Stage 3: pulmonary infiltrates without lymphadenopathy (15% of patients with active disease)
- Stage 4: fibrosis and end-stage lung disease (up to 20% of patients may progress to this stage).

Radiographic evaluation of sarcoidosis has been enhanced by high-resolution computed tomography (CT). Honeycombing, apical fibrocystic disease, and giant bullous emphysema are frequently encountered. The characteristic "fairy-ring" lesion, in which granulomas form rings of different sizes in the posterior lung fields, has been described on CT scan. Another sign ascribed to sarcoid on chest x-ray is the "pawnbroker's sign" of right paratracheal and bilateral hilar adenopathy. There is no "gold standard" of diagnosis but only support for the diagnosis. Lung biopsy is very accurate, but it is invasive and has attendant complications. Fine-needle aspiration biopsy is used by some and could replace the more costly surgical excision. Conjunctival biopsy is positive in approximately 70% of patients regardless of the presence of clinical eye involvement. Moreover, lacrimal gland biopsy is positive in 25% of patients with nonenlarged glands and in 75% with enlarged glands.

Half of patients with sarcoidosis exhibit abnormal liver function tests, and hypergammaglobulinemia is encountered in 70%. Other less specific tests include nuclear antibodies in 25%, cutaneous anergy in 40%, and increased levels of ACE seen in at least 50%. ACE has been detected in the cytoplasm of epithelioid granulomas in patients with clinical sarcoidosis (2). ACE elevation is not specific to sarcoidosis, so its diagnostic value should be tempered with clinical judgment. Hypercalcemia and hypercalciuria, occurring in about 10% and about 30% of patients, respectively, are due to dysregulated production of calcitriol. The hormone is released from activated macrophages in pulmonary alveoli with granulomatous inflammation (16). When present, this persistent hypercalcemia and hypercalciuria can lead to kidney stones and renal failure. This was, perhaps, the patient's misfortune in Hutchinson's first case of sarcoidosis 120 years ago.

DIFFERENTIAL DIAGNOSIS

Several conditions should enter into the differential diagnosis of sarcoidosis. Infections with noncaseating granuloma formation should be ruled out. These would typically show areas of necrosis. Parts of obtained specimens should be sent for culture and microscopic examination for fungi and acid-fast bacilli. Occupational disease such as berylliosis should be ruled out. In berylliosis, erythema nodosum is absent, the beryllium patch test is positive, serum ACE levels are normal, and laser microprobe mass spectrometry reveals the presence of beryllium metal in the lungs. Hypersensitivity pneumonitis is frequently misdiagnosed as sarcoidosis, but the granulomas associated with pneumonitis are interstitial and do not follow the lymphatics as in sarcoid. Bronchogenic carcinoma may evoke sarcoidlike histologic changes in lung parenchyma away from the tumor and regional lymph nodes. Pulmonary fibrosis may be confused with sarcoidosis in cases of fibrosing alveolitis and bronchiectasis, but the latter conditions lack the residual granulomas that usually persist through end-stage sarcoidosis (2).

The eyes are involved in 30% of patients with systemic sarcoidosis. A variant of sarcoid called Heerfordt's syndrome (uveoparotid fever) is characterized by fever, parotid enlargement, and uveitis. This constellation of symptoms was originally ascribed to mumps. Anterior segment lesions involve the conjunctiva, episclera, and sclera. Ocular sarcoid may be acute or chronic, with iridocyclitis, vitreous changes, periphlebitis, and retinal and choroidal granulomata affecting the majority of ocular tissue.

TREATMENT

Organ system treatment varies, but steroids are given for symptom control; the lowest effective dose of steroids is sought to minimize toxic effects.

Nasal involvement in sarcoid tends to follow a prolonged but benign course. Local measures such as topical steroids tend to minimize obstructive symptoms (17). Smooth, red papules and plaques on the nose and acral areas such as fingers, toes, and ears occur in lupus pernio, a subtype of sarcoidosis with a more aggressive course. Subcutaneous sarcoidosis is rare but can be disfiguring and lead to massive infection. The skin covering the nodules is frequently bluish and tends to ulcerate. Corticosteroids are the treatment of choice in disfiguring lesions, but if corticosteroids are contraindicated, methotrexate or hydroxychloroquine may be considered as alternatives. Allopurinol (200 mg/day) has been used with varying degrees of initial regression,

but disease treated with allopurinol usually progresses within 6 months (18).

Heart involvement usually presents as arrhythmia, most commonly ventricular tachycardia. Left ventricular function may be impaired, with marked diminution of ejection fraction due to pericardial effusion. Combined therapy with steroids, digitalis, and an angiotensin-1 receptor antagonist will usually effect improvement of both symptoms and objective parameters (19).

Neurosarcoidosis is an uncommon but sometimes life-threatening manifestation that may occur in up to 5% of patients. Facial nerve involvement is the most frequent presentation. Because it is usually seen in those with active disease, corticosteroid therapy is given as first-line treatment; an immunosuppressive medication is added in treatment failure (20). Adjunctive radiation therapy with low-dose cranial irradiation has given symptom relief with minimal side effects (21).

Vertebral or other bony involvement may be resistant to corticosteroid therapy. Long-term remission may be achieved with weekly methotrexate therapy (10 mg/wk). This agent is the only alternative that has been shown effective in chronic sarcoidosis with bony involvement, but long-term treatment carries a cumulative risk of hepatotoxicity (22).

The treatment of acute pulmonary sarcoidosis begins with corticosteroids, although the optimal dosing has not been determined. The typical initial dose is 30 to 40 mg/day, although up to 1 mg/kg/day has been used. If the patient has a concomitant neurologic, heart, or severe ocular lesion, the higher dose may be warranted. When symptoms improve, usually within 1 month, tapering should be initiated. Patients should be monitored after cessation of therapy to ensure arrest of the disease process. Relapse occurs in 20% to 50% of patients, and reinstitution of high-dose corticosteroids for 2 to 6 weeks is justified (23).

For pulmonary sarcoidosis stage 2 or 3, short-term use of inhaled steroids (budesonide 0.8 to 1.2 mg/day) may improve symptoms (mainly cough) but effect no improvement in the appearance of the chest x-ray or in lung function. Oral steroids are indicated in patients with stage 2 or 3 disease who have moderate to severe or progressive symptoms and chest x-ray changes as outlined above (24).

In patients with chronic sarcoidosis, unacceptably high doses of steroids are required to achieve symptom relief. In these cases, a corticosteroid-sparing drug may allow long-term treatment without the adverse effects of corticosteroids. Azathioprine (2 mg/kg body weight) may be effective in long-term therapy. Improvement occurs at induction and probably results from a reduction in cytokine activity (25).

Lung transplantation is reserved for end-stage refractory disease in "corticosteroid failures" (23).

SARCOIDOSIS IN THE PREGNANT PATIENT

Fertility is not affected in sarcoidosis, but elective pregnancy should be discouraged during active disease progression. However, pregnancy itself does not aggravate sarcoidosis, and the pregnancy is usually carried to term with no specific risk to the fetus from the disease. Therapeutic indications are the same, corticosteroids being the only proven treatment during this period. Methotrexate has teratogenic effects and should be avoided especially during heart development (from week 6 to week 8 of gestation). A flare at 3 to 6 months after delivery is not unusual (26).

SARCOIDOSIS IN CHILDREN

Sarcoidosis in children is uncommon, and recovery is more frequent than in adults. Corticosteroids and immunosuppressive treatment are the mainstays of therapy (27).

CONCLUSION

The common denominator in sarcoidosis seems to be the susceptible individual with an increased local cell-mediated immune response to unknown antigens.

Data suggest that sarcoid does not represent generalized depression of the immune system but rather a heightened inflammatory reaction at sites of active disease. The initial lesion arises as a result of an exaggerated local cell-mediated immune response to an unknown stimulus. Such a reaction involves the accumulation and compartmentalization of mononuclear cells in the lung parenchyma, setting up a milieu for granuloma formation. So for all we know, sarcoid remains a mystery whose diagnosis relies on the clinical synthesis of several pieces of information.

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